

R76-132

Reprinted from

TECHNICAL LIBRARY  
U.S. ARMY NATICK DEVELOPMENT CENTER  
01760

*Carbohydrate Research*, 45 (1975) 341-354  
© Elsevier Scientific Publishing Company, Amsterdam - Printed in Belgium

## SYNTHESIS OF BRANCHED-CHAIN, PYRROLIDINO-SUGAR DERIVATIVES RELATED TO APIOSE\*†

D. H. BALL, F. H. BISSETT, M. H. HALFORD‡, AND L. LONG, JR.

*Food Sciences Laboratory, U.S. Army Natick Development Center, Natick, Massachusetts 01760 (U. S. A.)*

(Received June 18th, 1975; accepted for publication, July 26th, 1975)

### ABSTRACT

3-C-(Acetamidomethyl)-1,2-*O*-isopropylidene- $\beta$ -L-threofuranose (**4**) and the 3-acetate (**5**) have been prepared in high yields from mono-*O*-isopropylidene-D-apiose [3-C-(hydroxymethyl)-1,2-*O*-isopropylidene- $\beta$ -L-threofuranose] (**1**). Acid-catalyzed methanolysis of **4** caused migration of the isopropylidene group and the formation of methyl 4-acetamido-4-deoxy-3-C-(hydroxymethyl)-2,3-*O*-isopropylidene- $\beta$ -D-erythro-furanoside (**8**) in 25% yield. The major product (45%) from the acetolysis of **4** was also a pyrrolidine derivative, namely, 4-acetamido-3-C-(acetoxymethyl)-1-*O*-acetyl-4-deoxy-2,3-*O*-isopropylidene- $\beta$ -D-erythro-furanose (**10**). Acetolysis of **5** removed the isopropylidene group and gave four acetylated pyrrolidines (isomeric at C-1 and C-2). Conditions which resulted in minimal epimerization at C-2 were established, and the major isomers **12** and **13** were isolated in reasonable yields.  $^1\text{H}$ - and  $^{13}\text{C}$ -n.m.r. data for equilibrium solutions of the pyrrolidines, and for intermediates **1-5**, are given.

### INTRODUCTION

Since publication in 1962 of the first syntheses of sugar derivatives containing nitrogen as the hetero-atom in the ring<sup>3,4</sup>, there has been a sustained interest in this class of compounds, particularly by Paulsen and his co-workers<sup>5,6</sup>. A logical extension of previous studies in this laboratory concerning the branched-chain sugar apiose<sup>7-9</sup> and its 4-thio analog<sup>1,10</sup> was the preparation of analogs of apiose in which nitrogen was the ring hetero-atom. 3-C-(Hydroxymethyl)-1,2-*O*-isopropylidene- $\beta$ -L-threofuranose<sup>7</sup> (**1**)<sup>8</sup>, which can be obtained in good yield from di-*O*-isopropylideneapiose, appeared to be especially suitable as a starting material since appropriate nitrogen

\*Dedicated for the memory of Dr. Hewitt G. Fletcher, Jr.

†Apiose: Part VII. For Part VI, see Ref. 1. For a preliminary report of part of this work, see Ref. 2.

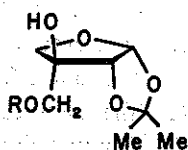
‡Present address: Carlton and United Breweries Ltd., Box 753F, GPO, Melbourne 3001, Australia.

<sup>8</sup>The apiofuranose terminology suggested by Cahn (see Ref. 11), and which was used in previous papers in this series, has been abandoned in favor of more systematic nomenclature. In the Cahn system, "the mirror image of a particular isomer is that in which all three stereochemical prefixes are simultaneously reversed" (e.g.,  $\alpha$ -D-D  $\rightarrow$   $\beta$ -L-L). This is not consistent with carbohydrate nomenclature and would lead to confusion when L-apiose derivatives are considered.

(or sulfur) functionality may be readily introduced at the 3<sup>1</sup>-position. Subsequent removal of the isopropylidene group would permit ring closure on nitrogen. This paper describes the preparation of a variety of pyrrolidino-sugars, most of which were synthesized with a view to their subsequent incorporation into nucleosides.

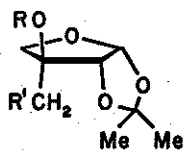
#### DISCUSSION

Selective *p*-toluenesulfonylation of **1** was carried out as previously described<sup>8</sup>, but on a larger scale, and, with subsequent chromatographic fractionation of mother liquors, the *p*-toluenesulfonate **2** was obtained in 96% yield. Treatment of **2** with sodium azide in boiling, aqueous acetone resulted in a clean nucleophilic displacement and 3-*C*-(azidomethyl)-1,2-*O*-isopropylidene- $\beta$ -L-threofuranose (**3**) was obtained crystalline in almost quantitative yield. Reduction of **3** with Raney nickel as catalyst, followed by *N*-acetylation, gave the crystalline 3-*C*-(acetamidomethyl) derivative **4** in good yield. Treatment of **4** with pyridine-acetic anhydride at 70° resulted in slow acetylation of the tertiary hydroxyl group. The *N,O*-diacetyl derivative **5** was obtained in good yield; a syrupy minor product, which was not fully characterized, appeared, by p.m.r. spectroscopy, to be the corresponding *N,N,O*-triacetyl derivative.



**1** R = H

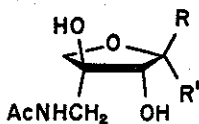
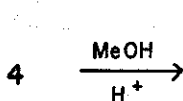
**2** R = Ts



**3** R = H, R' = N<sub>3</sub>

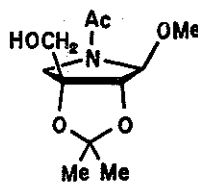
**4** R = H, R' = NHAc

**5** R = Ac, R' = NHAc



**6** R = OMe, R' = H (40%)

**7** R = H, R' = OMe (15%)

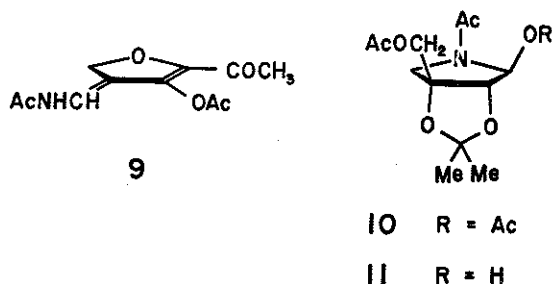


**8** (25%)

The major product isolated after acid-catalysed methanolysis of **4** was not a pyrrolidine. After chromatography of the mixture, methyl 3-*C*-(acetamidomethyl)- $\alpha$ -L-threofuranoside (**6**) and the  $\beta$ -anomer **7** were obtained in yields of 40 and 15%,

respectively. A preference for ring-closure on oxygen was not surprising since amide mesomerism renders acylamido groups less nucleophilic than hydroxyl groups<sup>6</sup>. A third product, isolated crystalline in 25% yield, still contained an isopropylidene group and was identified as the pyrrolidine, methyl 4-acetamido-4-deoxy-3-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene- $\beta$ -D-erythrofuranoside (8). The acetal migration from 1,2 $\rightarrow$ 2,3 is analogous with those previously found in acid-catalyzed methanolyses of **1**<sup>9</sup> and of the 3<sup>1</sup>-thio-analog of **1**<sup>1,10</sup> and, in this case, probably provides a "driving-force" for ring-closure on nitrogen.

Acetolysis of **4** appeared to be a more-attractive route to pyrrolidines, since it seemed likely that acylation of the primary hydroxyl group would force ring closure on nitrogen<sup>12,13</sup>. Treatment of **4** with acetic anhydride-acetic acid-sulfuric acid (25:25:1) at room temperature gave mainly pyrrolidines as expected, although the major product (45%), rather surprisingly, still contained an isopropylidene group. Intramolecular acetal migration had again occurred, and the product was identified as 4-acetamido-3-*C*-(acetoxymethyl)-1-*O*-acetyl-4-deoxy-2,3-*O*-isopropylidene- $\beta$ -D-erythrofurano-**10**. A mixture of acetylated pyrrolidine isomers was also formed together with a small proportion of a crystalline, unsaturated compound. This gave a molecular ion at 239 in the mass spectrum and an elemental analysis corresponding to C<sub>11</sub>H<sub>13</sub>NO<sub>5</sub>. Three acetyl groups were indicated by p.m.r. spectroscopy, and there was an Amide II band in the infrared spectrum. A non-zero specific rotation precluded a furan structure, and the ultraviolet absorption maximum and mass-spectral fragmentation data were consistent with the dihydrofuran derivative **9**.

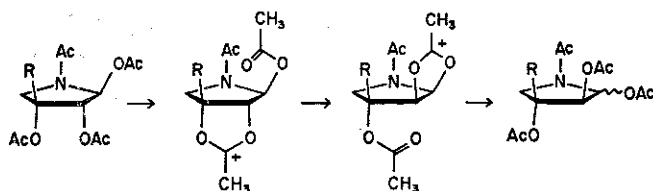


In a subsequent acetolysis of **4**, the mixture was worked up by pouring into ice-water (instead of excess of aqueous sodium hydrogen carbonate). The acidity of these conditions was sufficient to cause de-acetylation at C-1, and the major product was 4-acetamido-3-*C*-(acetoxymethyl)-4-deoxy-2,3-*O*-isopropylidene- $\beta$ -D-erythrofurano-**11**. Acetylation of **11** with pyridine-acetic anhydride gave **10** in good yield.

Variable-temperature p.m.r. spectroscopy has been used<sup>14</sup> to determine the activation parameters for conformational isomerism in **10**. Rate data derived from total line-shape analysis and from direct equilibration at low temperatures were in good agreement. Since the stereochemistry of crystalline **10** has also been established<sup>15</sup>, it is now possible to make unambiguous assignments in the p.m.r. spectra. These data

are recorded in Table II, and the rotamers have been designated as *Z* or *E* based on the sequence rule<sup>16</sup>. The crystalline conformer of **10**, which has the acetamido methyl group on the same side of the C-N bond as the anomeric carbon, and which was termed *cis* by Lipscomb, is thus the *E* rotamer.

Although **10** appeared to be a suitable intermediate for nucleoside synthesis, there were advantages to be gained by using pyrrolidine intermediates which did not contain the stable 2,3-*O*-isopropylidene group. Acetolysis of the *N,O*-diacetyl derivative **5** was therefore investigated, since, with this compound, migration of the isopropylidene group is no longer possible. Preliminary small-scale experiments indicated that the major products were acetylated pyrrolidines together with small proportions of the *C,N,O*-triacetyl derivative **9** and of the  $\alpha$  and  $\beta$  triacetates of 3-*C*-(acetamidomethyl)-L-threofuranose. The mixture of pyrrolidines was more complex than anticipated, since four isomers were detected. The additional isomers were clearly due to inversion at the central carbon atom of a *cis-trans* arrangement of three contiguous acetoxyl groups. Inversions of this type in acetolyzing media<sup>17,18</sup> probably occur *via* cyclic five-membered acetoxonium ions of furanose derivatives (Scheme 1).

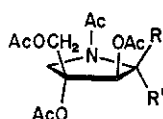
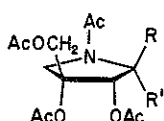


Scheme 1



The relative amounts of pyrrolidines formed were dependent on the relative concentrations of acetic anhydride and acetic acid. After a number of small-scale experiments, it was determined that (a) initial hydrolysis of the isopropylidene group and (b) an acetolyzing mixture of acetic anhydride-acetic acid-sulfuric acid (90:10:1) gave the best yields of the major isomers. Higher, relative concentrations of acetic acid led to lower proportions of these isomers, and since high concentrations of acetic acid favour the epimerization<sup>18</sup>, it seemed highly probable that the major isomers were not inverted at C-2. This was confirmed by acid hydrolysis of **5** and acetylation of the products with pyridine-acetic anhydride, conditions which could not lead to inversion at C-2. Although the pyrrolidine fraction comprised less than 20% of the mixture, it was shown, by p.m.r. spectroscopy, to contain two isomers only; these corresponded to the major isomers obtained from the large-scale acetolysis.

Chromatographic fractionation of the acetolysis products gave **9** (10%) and the crystalline pyrrolidine isomers **12**, **13**, and **15** in yields of 20, 10, and 2%, respectively. The mother liquors from the crystallization of **12** were found, by p.m.r. spectroscopy, to contain 25-30% of the fourth pyrrolidine isomer **14**. This indicates formation of **14** in < 2% yield.



12 R = OAc, R' = H

14 R = OAc, R' = H

13 R = H, R' = OAc

15 R = H, R' = OAc

The p.m.r. data for equilibrium solutions of the pyrrolidines are summarized in Table II, and typical behaviour under variable temperature conditions is shown in Fig. 1 for the H-1 and H-2 regions in the spectrum of **12**.  $^{13}\text{C}$ -N.m.r. data are summarized in Table III. Assignments were facilitated by single-frequency, off-resonance decoupling and by selective, single-frequency, heteronuclear decoupling<sup>19,20</sup> techniques.

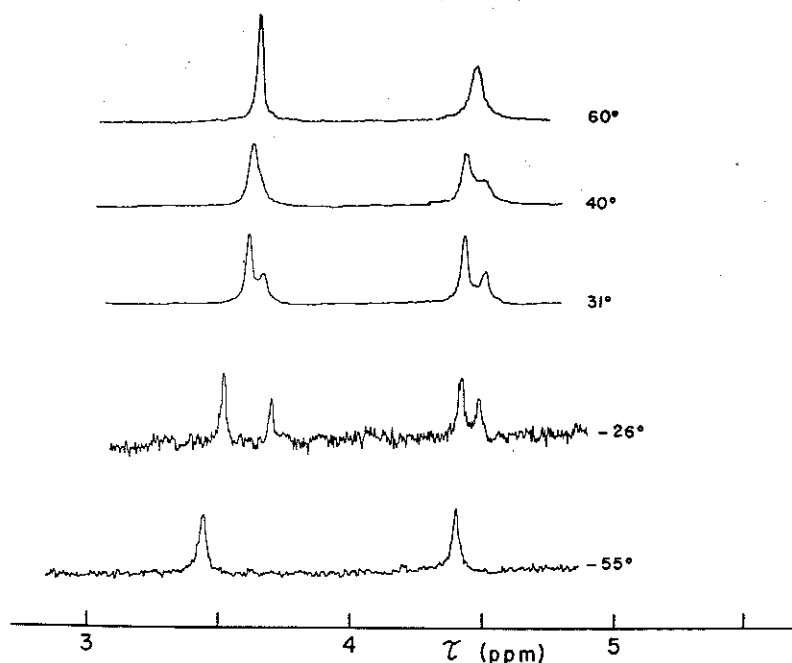


Fig. 1. Partial 100-MHz p.m.r. spectra of **12** in  $\text{DCON}(\text{CD}_3)_2$ , showing the H-1 and H-2 signals. The spectrum at  $-55^\circ$  was obtained after dissolution of crystalline **12** at *ca.*  $-60^\circ$ .

#### EXPERIMENTAL

*General methods.* — Solutions were concentrated under diminished pressure below  $50^\circ$ . Melting points were determined in glass capillaries with a Thomas-Hoover apparatus, and optical rotations were measured with a Bendix Ericsson

TABLE I

<sup>1</sup>H-N.M.R. SPECTRAL DATA<sup>a</sup> FOR THE THREOFURANOSE DERIVATIVES 1-7

Compound	Solvent	Chemical shifts in $\tau$ values (first-order couplings in parentheses)			
		H-1	H-2	H-4,4'	H-3 <sup>1</sup> ,3 <sup>1a</sup> Other
3-C-(Hydroxymethyl)-1,2-O-isopropylidene- $\beta$ -L-threofuranose (1)	(CD <sub>3</sub> ) <sub>2</sub> CO	4.13 d (J <sub>1,2</sub> 3.5)	5.68 d	— 6.04-6.50 m	5.87 s (OH); 8.56 s, 8.72 s (CMe <sub>2</sub> )
1,2-O-Isopropylidene-3-C-( <i>p</i> -toluenesulfonyloxymethyl)- $\beta$ -L-threofuranose (2)	CDCl <sub>3</sub>	4.06 d (J <sub>1,2</sub> 3.5)	5.72 d	6.18 s	5.75 s 2.12-2.76 (aryl); 7.54 s (ArMe); 8.59 s, 8.73 s (CMe <sub>2</sub> )
3-C-(Azidomethyl)-1,2-O-isopropylidene- $\beta$ -L-threofuranose (3)	CDCl <sub>3</sub>	4.02 d (J <sub>1,2</sub> 3.5)	5.65 d	6.10, 6.18 ABq (J <sub>4,4'</sub> 9.5)	6.27, 6.51 ABq (J <sub>3<sup>1</sup>,3<sup>1a</sup></sub> 12.5)
3-C-(Acetamidomethyl)-1,2-O-isopropylidene- $\beta$ -L-threofuranose (4)	CDCl <sub>3</sub>	4.04 d (J <sub>1,2</sub> 3.5)	5.70 d	6.10, 6.22 ABq (J <sub>4,4'</sub> 9)	6.28, 6.58 m <sup>b</sup> (J <sub>3<sup>1</sup>,3<sup>1a</sup></sub> 14.5, J <sub>3<sup>1</sup>,NH</sub> 6.5, J <sub>3<sup>1a</sup>,NH</sub> 5.5)
3-C-(Acetamidomethyl)-3-O-acetyl-1,2-O-isopropylidene- $\beta$ -L-threofuranose (5)	CDCl <sub>3</sub>	4.07 d (J <sub>1,2</sub> 3.5)	5.39 d	5.58, 6.04 ABq (J <sub>4,4'</sub> 10.5)	5.60, 6.50 m <sup>b</sup> (J <sub>3<sup>1</sup>,3<sup>1a</sup></sub> 14.5, J <sub>3<sup>1</sup>,NH</sub> 8.5, J <sub>3<sup>1a</sup>,NH</sub> 4.5)
Methyl 3-C-(acetamidomethyl)- $\alpha$ -L-threofuranoside (6)	C <sub>5</sub> H <sub>5</sub> N	4.40 s (J <sub>1,2</sub> ~1)	5.54 s	5.71, 5.81 ABq (J <sub>4,4'</sub> 9)	5.92, 6.28 m <sup>b</sup> (J <sub>3<sup>1</sup>,3<sup>1a</sup></sub> 14, J <sub>3<sup>1</sup>,NH</sub> 6, J <sub>3<sup>1a</sup>,NH</sub> 6)
Methyl 3-C-(acetamidomethyl)- $\beta$ -L-threofuranoside (7)	C <sub>5</sub> H <sub>5</sub> N	4.70 d (J <sub>1,2</sub> 4)	5.45 d	— 5.55-6.00 m	6.57 s (OMe); 7.97 s (NAC)

<sup>a</sup> Apparent first-order couplings are given in Hz; peak multiplicities: d, doublet; m, multiplet; ABq, AB quartet; s, singlet. <sup>b</sup> The AB portion of an ABX system; calculated couplings and chemical shifts are given.

TABLE II

<sup>1</sup>H-N.M.R. SPECTRAL DATA<sup>a</sup> FOR THE PYRROLIDINO-SUGARS 8 AND 10-15

Compound	Solvent	Chemical shifts in $\tau$ values
----------	---------	----------------------------------

TABLE II

<sup>1</sup>H-N.M.R. SPECTRAL DATA<sup>a</sup> FOR THE PYRROLIDINO-SUGARS **8** AND **10-15**

Compound	Solvent	Rotamer <sup>b</sup>	Chemical shifts in $\tau$ values (first-order couplings in parentheses)				
			H-1	H-2	H-4,4'	H-3 <sup>1,3</sup> ia	Other
Methyl 4-acetamido-4-deoxy-3-C-(hydroxymethyl)-2,3-O-isopropylidene- $\beta$ -D-erythrofuranoside ( <b>8</b> )	CDCl <sub>3</sub>	E (55%) Z (45%)	5.02s ( <i>J</i> <sub>1,2</sub> <0.5) 4.46s ( <i>J</i> <sub>1,2</sub> <0.5)	5.60s  5.73s	—  5.95-6.82m	—	6.66s, 6.64s (OMe); 7.84s, 7.92s (NAc); 8.55-8.77m (CMe <sub>2</sub> )
4-Acetamido-3-C-(acetoxymethyl)-1-O-acetyl-4-deoxy-2,3-O-isopropylidene- $\beta$ -D-erythrofuranoside ( <b>10</b> )	CDCl <sub>3</sub>	E (80%) Z (20%)	3.64 ( <i>J</i> <sub>1,2</sub> <0.5) 3.42 ( <i>J</i> <sub>1,2</sub> <0.5)	5.61s ( <i>J</i> <sub>1,2</sub> <0.5) 5.71s ( <i>J</i> <sub>1,2</sub> <0.5)	5.95, 6.57 ABq ( <i>J</i> <sub>4,4'</sub> 13) 6.27s	5.64, 5.80 ABq ( <i>J</i> <sub>3<sup>1,3</sup>ia</sub> 11)	7.83s, 7.90s, 7.92s (NAc, 2OAc); 8.58s, 8.60s (CMe <sub>2</sub> )
4-Acetamido-3-C-(acetoxymethyl)-4-deoxy-2,3-O-isopropylidene- $\beta$ -D-erythrofuranoside ( <b>11</b> )	(CD <sub>3</sub> ) <sub>2</sub> SO	E (80%) Z (20%)	4.64d ( <i>J</i> <sub>1,OH</sub> 4.5) <i>J</i> <sub>1,2</sub> <0.5 4.47d ( <i>J</i> <sub>1,OH</sub> 4.5) <i>J</i> <sub>1,2</sub> <0.5)	5.67s  5.76s	6.32, 6.64 ABq ( <i>J</i> <sub>4,4'</sub> 13) 6.37s	5.60, 5.88 ABq ( <i>J</i> <sub>3<sup>1,3</sup>ia</sub> 12)	3.69d (OH <sub>E</sub> ); 3.81d (OH <sub>Z</sub> ); 7.88-8.05m (NAc, OAc); 8.67s (CMe <sub>2</sub> )
4-Acetamido-3-C-(acetoxymethyl)-1,2,3-tri-O-acetyl-4-deoxy- $\beta$ -D-erythrofuranoside ( <b>12</b> )	CDCl <sub>3</sub>	E (65%) Z (35%)	3.72s ( <i>J</i> <sub>1,2</sub> <1) 3.55s ( <i>J</i> <sub>1,2</sub> <1)	4.48s  4.57d	5.91, 6.17 ABq ( <i>J</i> <sub>4,4'</sub> 14) 5.85, 6.19 ABq ( <i>J</i> <sub>4,4'</sub> 11)	5.22, 5.46 ABq ( <i>J</i> <sub>3<sup>1,3</sup>ia</sub> 12) 5.05, 5.59 ABq ( <i>J</i> <sub>3<sup>1,3</sup>ia</sub> 12)	7.80-8.00m (NAc, 4OAc)
4-Acetamido-3-C-(acetoxymethyl)-1,2,3-tri-O-acetyl-4-deoxy- $\alpha$ -D-erythrofuranoside ( <b>13</b> )	CDCl <sub>3</sub>	E (75%) Z (25%)	3.44d ( <i>J</i> <sub>1,2</sub> 5) 3.29d ( <i>J</i> <sub>1,2</sub> 5)	4.57d  4.24d	5.78, 6.20 ABq ( <i>J</i> <sub>4,4'</sub> 14) 5.76, 6.16 ABq ( <i>J</i> <sub>4,4'</sub> 14)	5.34, 5.52 ABq ( <i>J</i> <sub>3<sup>1,3</sup>ia</sub> 12)	7.80-7.95m (NAc, 4OAc)
4-Acetamido-3-C-(acetoxymethyl)-1,2,3-tri-O-acetyl-4-deoxy- $\beta$ -D-threofuranose ( <b>14</b> ) <sup>c</sup>	CDCl <sub>3</sub>	E (80%) Z (20%)	3.40d ( <i>J</i> <sub>1,2</sub> 5.5) 3.24d ( <i>J</i> <sub>1,2</sub> 5.5)	4.24d  4.32d	—  4.95-6.30m	—	7.80-8.00m (NAc, 4OAc)
4-Acetamido-3-C-(acetoxymethyl)-1,2,3-tri-O-acetyl-4-deoxy- $\alpha$ -D-threofuranose ( <b>15</b> )	CDCl <sub>3</sub>	E (75%) Z (25%)	3.75s ( <i>J</i> <sub>1,2</sub> <1) 3.60s ( <i>J</i> <sub>1,2</sub> <1)	4.33s  4.36s	5.90, 6.07 ABq ( <i>J</i> <sub>4,4'</sub> 13) 5.77, 6.09 ABq ( <i>J</i> <sub>4,4'</sub> 11)	5.41s	7.80-7.95m (NAc, 4OAc)

<sup>a</sup> Apparent first-order couplings are given in Hz; peak multiplicities: d, doublet, m, multiplet; ABq, AB quartet; s, singlet. <sup>b</sup> The approximate percentages of each rotamer in the equilibrium mixture are given in parentheses. <sup>c</sup> Values are taken from the spectrum of a mixture containing **12** and **14**.

TABLE III  
<sup>13</sup>C-N.M.R. CHEMICAL SHIFTS FOR COMPOUNDS 1-5, 10-13, AND 15

Compound	Chemical shifts on the $\delta$ scale <sup>a</sup>							
	C-1	C-2	C-3	C-4	C-3'	CMe <sub>2</sub>	CMe <sub>2</sub>	CH <sub>3</sub> CO
3-C-(Hydroxymethyl)-1,2-O-isopropylidene- $\beta$ -L-threofuranose (1)	109.11	87.97	83.49	77.67	65.83	115.16	30.82	
1,2-O-Isopropylidene-3-C-( <i>p</i> -toluenesulfonyloxymethyl)- $\beta$ -L-threofuranose (2)	109.93	87.79	84.29	77.01	74.58	116.54	30.49	
3-C-(Azidomethyl)-1,2-O-isopropylidene- $\beta$ -L-threofuranose (3)	109.83	87.98	85.56	77.40	56.62	116.63	30.59	
3-C-(Acetamidomethyl)-1,2-O-isopropylidene- $\beta$ -L-threofuranose (4)	109.57	88.14	85.29	77.82	45.90	115.94	30.36	26.17
3-C-(Acetamidomethyl)-3-O-acetyl-1,2-O-isopropylidene- $\beta$ -L-threofuranose (5)	109.08	86.38	93.18	74.61	42.01	116.12	30.12	26.23
							29.87	25.08
<i>Rotamer<sup>b</sup></i>								
4-Acetamido-3-C-(acetoxymethyl)-1-O-acetyl-4-deoxy-2,3-O-isopropylidene- $\beta$ -D-erythrofuranoose (10)	90.02	89.49	91.33	57.73	68.85	117.17	31.56	25.31
	89.49	89.15	92.70	60.02			30.49	24.38
4-Acetamido-3-C-(acetoxymethyl)-4-deoxy-2,3-O-isopropylidene- $\beta$ -D-erythrofuranoose (11)	89.64	90.70	91.19	57.39	69.82		31.66	25.93
	87.50	89.34	92.16	59.43	69.24	116.73	30.40	25.06
4-Acetamido-3-C-(acetoxymethyl)-1,2,3-tri-O-acetyl-4-deoxy- $\beta$ -D-erythrofuranoose (12)	87.69	79.54	85.27	55.45	66.04			24.2
	85.65	77.88	86.24	56.23				
4-Acetamido-3-C-(acetoxymethyl)-1,2,3-tri-O-acetyl-4-deoxy- $\alpha$ -D-erythrofuranoose (13)	83.52	75.07	85.65	54.09	65.55			25.25
	81.57	74.10		55.35				24.28
4-Acetamido-3-C-(acetoxymethyl)-1,2,3-tri-O-acetyl-4-deoxy- $\alpha$ -D-threofuranose (15)	88.71	81.67	88.13	56.18	64.58			25.20
	87.98	80.60	88.71	56.81				24.38

<sup>a</sup>Chemical shifts, measured downfield from external Me<sub>4</sub>Si, are taken from proton noise-decoupled spectra of solutions in CDCl<sub>3</sub>; except for 1 which was examined in (CD<sub>3</sub>)<sub>2</sub>SO;  $\delta_{\text{CDCl}_3}$  = 80.87 p.p.m. <sup>b</sup>The *E*-rotamer was the major isomer in all cases except for 11: hydrogen bonding between the anomeric hydroxyl and the amide carbonyl may contribute to the stability of the *Z*-rotamer. In (CD<sub>3</sub>)<sub>2</sub>SO solution, the *E*-rotamer of 11 predominates (cf. Table II).



ETL-NPL automatic polarimeter equipped with a yellow (sodium) filter.  $^1\text{H-N.m.r.}$  spectra were recorded at 100 MHz with a Varian HA-100 spectrometer operating in the frequency-sweep mode with tetramethylsilane as the internal reference.  $^{13}\text{C-N.m.r.}$  spectra were obtained on the same instrument equipped with a Digilab FTS/NMR-3HC system, using 8-mm sample tubes. Mass spectra were measured with a Hitachi-Perkin-Elmer RMU-6D single-focussing spectrometer with an ionizing potential of 70 eV and an accelerating potential of 1.75 kV. Infrared spectra were recorded with a Perkin-Elmer Model 137 spectrophotometer and were calibrated against the  $1600\text{ cm}^{-1}$  band of polystyrene. Ascending t.l.c. was performed on Silica Gel GF, and developed plates were examined under u.v. light (where appropriate) and then sprayed successively with a 1% solution of 1-naphthol in ethanol and with sulfuric acid, and heated. Column chromatography was performed on silica gel (70–325 mesh, ASTM; E. Merck AG, Darmstadt, Germany; distributed by Brinkmann Instruments, Inc.).

**3-C-(Azidomethyl)-1,2-O-isopropylidene- $\beta$ -L-threofuranose (3).** — A solution of the *p*-toluenesulfonate **2**<sup>7</sup> (51.7 g, 0.15 mol) and sodium azide (39 g, 0.60 mol) in acetone (775 ml) and water (225 ml) was boiled under reflux. T.l.c. (ether) indicated complete conversion into **3** after 19 h, and concentration of the solution afforded a crystalline residue which was extracted with hot dichloromethane. Concentration of the dried ( $\text{Na}_2\text{SO}_4$ ) extracts gave a syrup which crystallized from carbon tetrachloride to give **3** (23.5 g). Fractionation of the mother liquors by chromatography on silica gel afforded additional crystalline material (total yield 31.8 g, 98%), m.p. 51.5–52.5°,  $[\alpha]_{\text{D}}^{25} +76^\circ$  (*c* 1.0, ethanol);  $\nu_{\text{max}}^{\text{KBr}}$  3450 (OH), 2100 ( $\text{N}_3$ ), 1375, and  $1385\text{ cm}^{-1}$  ( $\text{CMe}_2$ ). For n.m.r. data, see Tables I and III.

*Anal.* Calc. for  $\text{C}_8\text{H}_{13}\text{N}_3\text{O}_4$ : C, 44.65; H, 6.09; N, 19.53. Found: C, 44.65; H, 6.02; N, 19.71.

**3-C-(Acetamidomethyl)-1,2-O-isopropylidene- $\beta$ -L-threofuranose (4).** — To a solution of **3** (20 g) in methanol (200 ml) was added Raney nickel (~5 g wet; W. R. Grace & Co., No. 28), and hydrogen was bubbled through the stirred suspension. T.l.c. (ethyl acetate) indicated a smooth reduction which was complete after 4 h. The suspension was filtered, and the filtrate was concentrated to a syrup which was taken up in water (150 ml). Acetic anhydride (20 ml) was added to the stirred solution, and t.l.c. (acetone) indicated a rapid reaction (complete after a few minutes). Concentration of the solution afforded a syrup which was taken up in ethyl acetate, and the dried ( $\text{Na}_2\text{SO}_4$ ) solution was again concentrated. The residue crystallized and was recrystallized from ether to give **4** (17.8 g, 83%), m.p. 80.5–82°,  $[\alpha]_{\text{D}}^{25} +81^\circ$  (*c* 1.0, ethanol);  $\nu_{\text{max}}^{\text{KBr}}$  3300 (OH, NH), 1640 (Amide I), 1570 (Amide II), 1380, and  $1370\text{ cm}^{-1}$  ( $\text{CMe}_2$ ). For n.m.r. data, see Tables I and III.

*Anal.* Calc. for  $\text{C}_{10}\text{H}_{17}\text{NO}_5$ : C, 51.94; H, 7.41; N, 6.06. Found: C, 51.91; H, 7.33; N, 6.09.

**3-C-(Acetamidomethyl)-3-O-acetyl-1,2-O-isopropylidene- $\beta$ -L-threofuranose (5).** — Crude **4** (from 20 g of **3**) was dissolved in dry pyridine (150 ml). Acetic anhydride (17 ml, 2 equiv.) was added and the stirred solution was heated at 70°. T.l.c. (ethyl

acetate) indicated slow acetylation that was complete after 2 days. Solvents were removed by evaporation, and the residual syrup crystallized when diluted with ethanol; yield 16.6 g. Fractionation of the mother liquors on silica gel afforded additional crystalline material, and the combined product was recrystallized from ethyl acetate to give **5** (21.1 g, 83% from **3**), m.p. 109–111°,  $[\alpha]_D^{25} +148^\circ$  (*c* 1.0, ethanol);  $\nu_{\max}^{\text{KBr}}$  3300 (NH), 1750 (OAc), 1650 (Amide I), and 1560  $\text{cm}^{-1}$  (Amide II). For n.m.r. data, see Tables I and III.

*Anal.* Calc. for  $\text{C}_{12}\text{H}_{19}\text{NO}_6$ : C, 52.74; H, 7.01; N, 5.13. Found: C, 52.88; H, 7.09; N, 4.98.

*Methanolysis of 4.* — A solution of **4** (1.60 g) in methanolic hydrogen chloride (2% w/v, 100 ml) was kept at room temperature and examined at intervals by t.l.c. (ethyl acetate–ethanol, 5:1). After 3 days, a trace of **4** remained and three major products were indicated. The solution was neutralized by passage down a column of Dowex 1 ( $\text{HO}^-$ ) resin and then concentrated. The resultant syrup was fractionated on a column of silica gel (300 g) with chloroform–ethyl acetate (3:1).

Fraction *A* (0.42 g) crystallized after distillation ( $\sim 105^\circ/0.1$  torr). Recrystallization from carbon tetrachloride afforded pure methyl 4-acetamido-4-deoxy-3-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene- $\beta$ -D-erythrofuranoside (**8**), m.p. 61–63°,  $[\alpha]_D^{25} +9^\circ$  (*c* 1.0, chloroform);  $\nu_{\max}^{\text{KBr}}$  3400 (OH), 1620 (Amide I), 1385, and 1370  $\text{cm}^{-1}$  ( $\text{CMe}_2$ ). For n.m.r. data, see Tables II and III.

*Anal.* Calc. for  $\text{C}_{11}\text{H}_{19}\text{NO}_5$ : C, 53.87; H, 7.81; N, 5.71. Found: C, 53.57; H, 8.06; N, 5.84.

Fraction *B* (0.60 g) crystallized, and recrystallization from isopropyl ether–dichloromethane gave methyl 3-*C*-(acetamidomethyl)- $\alpha$ -L-threofuranoside (**6**), m.p. 135–136°,  $[\alpha]_D^{26} -121^\circ$  (*c* 1.0, methanol);  $\nu_{\max}^{\text{KBr}}$  1620 (Amide I) and 1580  $\text{cm}^{-1}$  (Amide II). For n.m.r. data, see Table I.

*Anal.* Calc. for  $\text{C}_8\text{H}_{15}\text{NO}_5$ : C, 46.82; H, 7.37; N, 6.83. Found: C, 46.61; H, 7.50; N, 6.76.

Fraction *C* (0.27 g) crystallized, and recrystallization from chloroform gave methyl 3-*C*-(acetamidomethyl)- $\beta$ -L-threofuranoside (**7**), m.p. 164–165°,  $[\alpha]_D^{26} +130^\circ$  (*c* 0.6, methanol);  $\nu_{\max}^{\text{KBr}}$  1620 (Amide I), and 1540  $\text{cm}^{-1}$  (Amide II). For n.m.r. data, see Table I.

*Anal.* Calc. for  $\text{C}_8\text{H}_{15}\text{NO}_5$ : C, 46.82; H, 7.37; N, 6.83. Found: C, 46.67; H, 7.41; N, 6.69.

*Acetolysis of 4.* — A solution of **4** (1.0 g) in acetic acid (25 ml) and acetic anhydride (25 ml) was stirred and cooled in an ice-bath. Conc. sulfuric acid (1 ml) was added dropwise and the solution was then kept at room temperature for 5 h. The reaction mixture was then slowly added to a stirred suspension of sodium hydrogen carbonate (85 g) in water (300 ml), and the resulting pale-yellow solution was extracted with chloroform (4  $\times$  100 ml). Examination of the dried ( $\text{MgSO}_4$ ) extracts by t.l.c. (ether) indicated a complex mixture of products. Chloroform was removed by evaporation and the resultant syrup was fractionated on a column of silica gel (200 g) with benzene–ether (3:1).

Fraction *A* (0.05 g) crystallized and, after recrystallization from ether, the unsaturated *C,N,O*-triacetyl derivative **9** had m.p. 126–126.5°,  $[\alpha]_D^{25} -4^\circ$  (*c* 0.5, chloroform);  $\nu_{\max}^{\text{KBr}}$  3270 (NH), 1750 (OAc), 1730 (CAc), 1630 (Amide I), and 1570  $\text{cm}^{-1}$  (Amide II);  $\lambda_{\max}^{\text{EtOH}}$  283 nm ( $\epsilon$  23,000); *m/e* 239 ( $\text{M}^+$ ), 197 ( $\text{M}-\text{CH}_2=\text{CO}$ ), 180 ( $\text{M}-\text{OAc}$ ), 179 ( $\text{M}-\text{AcOH}$ ), 154 ( $\text{M}-\text{CH}_2=\text{CO}-\text{CH}_3\text{CO}$ ), 137 (base peak,  $\text{M}-\text{CH}_2\text{CO}-\text{AcOH}$ ). P.m.r. data (chloroform-*d*):  $\tau$  0.74 (broad 1-proton singlet that disappeared on deuteration, NH), 2.99 (1-proton doublet, *J* ~ 4 Hz, that became a singlet on deuteration, =CH-NHAc), 5.09 (2-proton singlet, -CH<sub>2</sub>-), 7.60, 7.62, 7.94 (3-proton singlets, CAc, NAc, OAc).

*Anal.* Calc. for  $\text{C}_{11}\text{H}_{13}\text{NO}_5$ : C, 55.23; H, 5.48; N, 5.85. Found: C, 55.12; H, 5.40; N, 5.56.

Fraction *B* (0.63 g) was purified by Kugelrohr distillation at 110°/0.04 torr. The distillate crystallized, and recrystallization from ethanol afforded 4-acetamido-3-*C*-(acetoxymethyl)-1-*O*-acetyl-4-deoxy-2,3-*O*-isopropylidene- $\beta$ -D-erythrofurano-**10** as long needles, m.p. 85–87°,  $[\alpha]_D^{25} -32^\circ$  (*c* 1.0, chloroform);  $\nu_{\max}^{\text{KBr}}$  1750 (OAc), 1680 (Amide I), 1380, and 1370  $\text{cm}^{-1}$  ( $\text{CMe}_2$ ); no Amide II band. For n.m.r. data, see Tables II and III.

*Anal.* Calc. for  $\text{C}_{14}\text{H}_{21}\text{NO}_7$ : C, 53.33; H, 6.71; N, 4.44. Found: C, 53.46; H, 6.74; N, 4.42.

Fraction *C* (0.32 g) was a mixture of acetylated pyrrolidine isomers and was not further examined.

Acetolysis of **4** (3.0 g), using the above conditions except that acetone-*d*<sub>6</sub> (1.7 g) was added before the sulfuric acid, afforded, after chromatography, the same products in similar yields. No evidence for the incorporation of deuterium into **10** was obtained from the p.m.r. spectrum.

4-Acetamido-3-*C*-(acetoxymethyl)-4-deoxy-2,3-*O*-isopropylidene- $\beta$ -D-erythrofurano-**11**. — To a solution of **4** (40 g) in acetic acid (1200 ml) and acetic anhydride (160 ml), cooled to ~10°, sulfuric acid (60 ml) was slowly added. The solution was kept at room temperature for 30 min and then poured into stirred ice-water (2.5 l). The mixture was extracted with chloroform (2 × 1 litre, 2 × 500 ml), and the combined extracts were washed with water, saturated aqueous sodium hydrogen carbonate, and water (× 3). Concentration afforded a syrup which was dried by repeated evaporation with ethanol. The product crystallized, and recrystallization from ethyl acetate-ether gave **11** (18 g, 38%), m.p. 108–110°,  $[\alpha]_D^{25} +20^\circ$  (*c* 1.0, chloroform);  $\nu_{\max}^{\text{KBr}}$  3300 (OH), 1750 (OAc), 1630 (Amide I), 1380, and 1370  $\text{cm}^{-1}$  ( $\text{CMe}_2$ ); no Amide II band. For n.m.r. data, see Tables II and III.

*Anal.* Calc. for  $\text{C}_{12}\text{H}_{19}\text{NO}_6$ : C, 52.74; H, 7.01; N, 5.13. Found: C, 52.46; H, 7.18; N, 5.21.

Acetylation of **11** with acetic anhydride-pyridine gave **10** in good yield.

4-Acetamido-3-*C*-(acetoxymethyl)-1,2,3-tri-*O*-acetyl-4-deoxy-D-tetrafuranoses (**12**, **13**, **14**, **15**). — A solution of **5** (5.46 g, 20 mmol) in acetic acid (100 ml) and water (100 ml) was stirred at room temperature with Dowex 50 (W-x8, H<sup>+</sup>, 200–400 mesh) resin. After 1 week, t.l.c. (acetone) indicated the absence of **5**; the resin was then

removed by filtration and the filtrate was concentrated to a syrup. This was taken up in acetic acid (20 ml), and acetic anhydride (180 ml) followed by sulfuric acid (2 ml) were added. After 1 h at room temperature, the dark solution was added slowly to a stirred mixture of water (800 ml) and sodium hydrogen carbonate (300 g). After ~15 min, gas evolution had ceased and the solution was extracted with chloroform ( $4 \times 250$  ml). The dried ( $\text{MgSO}_4$ ) extracts were concentrated to a syrup (4.1 g) which was fractionated by chromatography on a column of silica gel (500 g) with ether.

Fraction *A* (0.50 g) crystallized, and recrystallization from ether gave material identical with **9**.

Fraction *B* (1.86 g) crystallized, and recrystallization from ether afforded the preponderant pyrrolidine isomer, 4-acetamido-3-*C*-(acetoxymethyl)-1,2,3-tri-*O*-acetyl-4-deoxy- $\beta$ -D-erythrofurano-**se** (**12**, 1.44 g), m.p. 98–101°,  $[\alpha]_D^{25} -29^\circ$  (*c* 1.06, chloroform);  $\nu_{\text{max}}^{\text{KBr}}$  1750 (OAc) and 1680  $\text{cm}^{-1}$  (Amide I), no Amide II band. For n.m.r. data, see Tables II and III.

*Anal.* Calc. for  $\text{C}_{15}\text{H}_{21}\text{NO}_9$ : C, 50.14; H, 5.89; N, 3.90. Found: C, 50.29; H, 5.98; N, 3.76.

Concentration of the mother liquors from the crystallization of **12** gave a syrup (0.42 g), and p.m.r. spectroscopy indicated that this contained, in addition to **12**, 25–30% of the  $\beta$ -D-*threo* isomer **14**. For partial n.m.r. data, see Table II.

Fraction *C* (0.15 g) crystallized, and recrystallization from ether yielded 4-acetamido-3-*C*-(acetoxymethyl)-1,2,3-tri-*O*-acetyl-4-deoxy- $\alpha$ -D-threofurano-**se** (**15**), m.p. 120–122.5°,  $[\alpha]_D^{25} -19^\circ$  (*c* 1.06, chloroform);  $\nu_{\text{max}}^{\text{KBr}}$  1750 (OAc) and 1675  $\text{cm}^{-1}$  (Amide I), no Amide II band. For n.m.r. data, see Tables II and III.

*Anal.* Calc. for  $\text{C}_{15}\text{H}_{21}\text{NO}_9$ : C, 50.14; H, 5.89; N, 3.90. Found: C, 50.13; H, 5.95; N, 3.77.

Fraction *D* (0.68 g) crystallized from ethanol, and recrystallization from the same solvent gave 4-acetamido-3-*C*-(acetoxymethyl)-1,2,3-tri-*O*-acetyl-4-deoxy- $\alpha$ -D-erythrofurano-**se** (**13**), m.p. 97–98°,  $[\alpha]_D^{25} -15^\circ$  (*c* 1.26, chloroform);  $\nu_{\text{max}}^{\text{KBr}}$  1750 (OAc) and 1675  $\text{cm}^{-1}$  (Amide I), no Amide II band. For n.m.r. data, see Tables II and III.

*Anal.* Calc. for  $\text{C}_{15}\text{H}_{21}\text{NO}_9$ : C, 50.14; H, 5.89; N, 3.90. Found: C, 50.12; H, 5.98; N, 3.74.

*Préparation of acetylated pyrrolidines under non-acetolyzing conditions.* — A solution of **5** (0.25 g) in acetic acid (5 ml) and water (5 ml) was stirred at room temperature with Dowex 50 (W-x8,  $\text{H}^+$ , 200–400 mesh) resin for 5 days. T.l.c. (acetone) then indicated the absence of **5**, the resin was removed by filtration, and the filtrate was lyophilized. The product was taken up in dry pyridine (6 ml), and acetic anhydride (2 ml) was added. After 5 days at room temperature, t.l.c. (ethyl acetate and ether) indicated no further reaction, solvents were then removed by evaporation, and the resultant syrup was fractionated by chromatography on silica gel (20 g) with ethyl acetate. The pyrrolidine fraction (0.06 g) was eluted first, and p.m.r. spectroscopy showed that approximately equal amounts of the  $\alpha$  and  $\beta$  isomers **12** and **13** were present. No trace of the C-2 inverted products **14** and **15** could be detected.

## REFERENCES

- 1 M. H. HALFORD, D. H. BALL, AND L. LONG, JR., *J. Org. Chem.*, 36 (1971) 3714-3719.
- 2 M. H. HALFORD, D. H. BALL, AND L. LONG, JR., *Chem. Commun.*, (1969) 255-256.
- 3 J. K. N. JONES AND J. C. TURNER, *J. Chem. Soc.*, (1962) 4699-4703.
- 4 H. PAULSEN, *Angew. Chem.*, 74 (1962) 901; *Angew. Chem. Int. Ed. Engl.*, 1 (1962) 597.
- 5 H. PAULSEN, *Angew. Chem.*, 78 (1966) 501-516; *Angew. Chem. Int. Ed. Engl.*, 5 (1966) 495-510.
- 6 H. PAULSEN AND K. TODT, *Advan. Carbohydr. Chem.*, 23 (1968) 115-232.
- 7 F. A. CAREY, D. H. BALL, AND L. LONG, JR., *Carbohydr. Res.*, 3 (1966) 205-213.
- 8 D. H. BALL, F. A. CAREY, I. L. KLUNDT, AND L. LONG, JR., *Carbohydr. Res.*, 10 (1969) 121-128.
- 9 D. H. BALL, F. H. BISSETT, I. L. KLUNDT, AND L. LONG, JR., *Carbohydr. Res.*, 17 (1971) 165-174.
- 10 M. H. HALFORD, D. H. BALL, AND L. LONG, JR., *Carbohydr. Res.*, 8 (1968) 363-365.
- 11 D. J. BELL, F. A. ISHERWOOD, N. R. HARDWICK, AND R. S. CAHN, *J. Chem. Soc.*, (1954) 3702-3706.
- 12 E. J. REIST, D. E. GUEFFROY, R. W. BLACKFORD, AND L. GOODMAN, *J. Org. Chem.*, 31 (1966) 4025-4030.
- 13 A. J. DICK AND J. K. N. JONES, *Can. J. Chem.*, 46 (1968) 425-434.
- 14 C. H. BUSHWELLER, J. W. O'NEIL, M. H. HALFORD, AND F. H. BISSETT, *Chem. Commun.*, (1970) 1251-1252; *J. Amer. Chem. Soc.*, 93 (1971) 1471-1473.
- 15 Y. H. CHIU AND W. N. LIPSCOMB, *J. Amer. Chem. Soc.*, 96 (1974) 978-982.
- 16 IUPAC 1968 Tentative Rules, Section E, Fundamental Stereochemistry, *J. Org. Chem.*, 35 (1970) 2849-2867.
- 17 P. JERKEMAN, *Acta Chem. Scand.*, 17 (1963) 2769-2771.
- 18 W. SOWA, *Can. J. Chem.* 49 (1971) 3292-3298; *ibid*, 50 (1972) 1092-1094.
- 19 A. J. JONES, T. D. ALGER, D. M. GRANT, AND W. M. LITCHMAN, *J. Amer. Chem. Soc.*, 92 (1970) 2386-2394.
- 20 N. S. BHACCA, F. W. WEHRLI, AND N. H. FISCHER, *J. Org. Chem.*, 38 (1973) 3618-3622.